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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,077	04/15/2004	Martin Stanton	23239-531 CIP	9984

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
12/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,077	STANTON ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) *5,7-9 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 27, 2007 has been entered.

Election/Restrictions

Claims 5, 7-9 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 24, 2006.

Claims 1, 4, 6, 10 and 13-18 are examined on the merits.

Claim Rejections - 35 USC § 103

Claims 1, 4, 6, 10 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warren in view of Holmes, Apelgren et al. and Virtanen et al. (all of record).

The claimed invention is directed to aptamer-toxin conjugates comprising aptamers conjugated to cytotoxic moieties that can be small molecule chemotherapeutic agent and can be covalently conjugated. In some embodiments the aptamers target tumor cells and the linker comprises nucleophilic or electrophilic moieties. Other embodiments recite the particular structures of the alkaloid vinblastine and the linkers.

Warren discloses at pages 17-18 prodrugs comprising an aptamer and a drug joined by a linker. Warren discloses at pages 26-27 that the drugs include vinca alkaloids. Example 5 describes use of the disclosed prodrugs to target cancerous cells. In table 4 Warren specifically teaches that the drug can be the vinca alkaloid vinblastine. At page 7 Warren teaches that aptamers have been used as an alternative to antibodies for the purpose of targeting therapeutic agents to cells. Warren does not explicitly teach aptamers targeted to PSMA, the use of the vinblastine analog desacetylvinblastine-3-carboxhydrazide or the use of linkers that comprise dendrimers.

Holmes teaches that PSMA is a transmembrane protein specific to prostate epithelial cells that is expressed at increased levels in cancerous cells. Holmes further teaches that this protein is an ideal sentinel molecule for targeting prostate cancer cells.

Apelgren et al. teach that antibodies conjugated to 4-desacetylvinblastine-3-carboxhydrazide were known in the art to regress adenocarcinoma and squamous carcinoma xenografts in athymic nude mice. Apelgren et al. extend the use of such conjugates to the treatment of ovarian cancer. Apelgren et al. teach that the use of the conjugated drug increased the survival of tumor bearing mice over treatment of the drug alone or a non-antigen binding immunoconjugate.

Virtanen et al. teach complexes containing a binding molecule such as an antibody, a joining component and a therapeutic molecule such as a drug. At column 10 Virtanen et al. teach that the joining component may be a bifunctional linker and may be a dendrimer type polymer.

It would have been obvious to one of ordinary skill in the art at the time of invention to make aptamer-drug conjugates as taught by Warren using an aptamer that targets PSMA. It would have been further obvious to use desacetyl-3-carboxhydrazide as the drug component of the conjugate and to use a dendrimer as the linker component. Holmes provides a motivation to target PSMA with therapeutic agents, teaching that this protein is preferentially expressed in prostate tissue and expressed at increased levels in cancerous cells. Warren explicitly teaches vinblastine as the drug component of an aptamer-drug conjugate and Apelgren et al. provide a motivation to use desacetylvinblastine-3-carboxhydrazide by teaching that immunoconjugates comprising this drug increase survival time of tumor bearing mice over those receiving the drug alone. Based the teachings of Virtanen et al. one of ordinary skill in the art would recognize that the use of a dendrimer linker is mere design choice made by the person of ordinary skill in order to produce a conjugate with the optimum properties for the desired application. One of ordinary skill in the art would have had a reasonable expectation of success in targeting PSMA with the conjugates taught by Warren because Warren teaches aptamer-drug conjugates, their general applicability and methods of synthesis. One of ordinary skill in the art would have had a reasonable expectation of success in making aptamer-drug conjugates comprising desacetylvinblastine-3-carboxhydrazide or dendrimers because Warren teaches the

production of aptamer-drug conjugates, Apelgren et al. teach the synthesis of conjugates comprising desacetylvinblastine-3-carboxhydrazide and Virtanen et al. teach that dendrimers are a known linking moiety that can be incorporated into a conjugate using known synthetic methods.

Thus, the invention of claims 1, 4, 6 10 and 13-18 would have been obvious, as a whole, at the time of invention.

Response to arguments

Applicants again traverse the 103 rejection by quoting a statement from the previously applied written description rejection and note that the examiner made this statement without disclaimer or qualification. Applicants ask why, if non-PSMA binding aptamers, already known in the art, would not inform one skilled in the art as to the structure of a PSMA binding aptamer; then how may the Holmes reference, which is completely silent on aptamers motivate one of skill in the art to produce conjugates comprising aptamers targeted to PSMA.

The Holmes reference provides a motivation to target PSMA therapeutically by teaching that this protein is preferentially expressed in prostate tissue and expressed at increased levels in cancerous cells. The motivation to use an aptamer to target a drug comes from the Warren reference.

The statement quoted by applicants is not an admission by the examiner and is not intended to validate the empirical nature of aptamer discovery. In fact, this statement was in fact invalidated when applicants provided arguments that successfully

rebutted this rejection. As applicants themselves argued, the SELEX process describes protocols required to generate aptamers against a variety of targets, including PSMA.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
December 22, 2007